

1
2
3
4
5 IN THE UNITED STATES DISTRICT COURT
6 FOR THE NORTHERN DISTRICT OF CALIFORNIA
7

8 SANOFI-AVENTIS DEUTSCHLAND GMBH,

No. C 08-4909 SI; C 09-4919 SI

9 Plaintiff,

ORDER RE: CLAIM CONSTRUCTION

10 v.

11 GENENTECH, INC. and BIOGEN IDEC INC.,

12 Defendants.
13 _____/

14 On May 11, 2010, the Court held a tutorial and a claim construction hearing. After consideration
15 of the parties' papers and presentations, the Court construes the claims at issue as follows.
16

17 **BACKGROUND**

18 On April 1, 2010, plaintiff Sanofi-Aventis Deutschland GmbH ("Sanofi") filed an amended
19 complaint against defendants Genentech, Inc. ("Genentech") and Biogen IDEC, Inc. ("Biogen"). Sanofi
20 alleges that Genentech and Biogen have infringed U.S. Patent No. 5,849,522 (the "522 patent"), entitled
21 "Enhancer for Eukaryotic Expression Systems," and U.S. Patent No. 6, 218,140 (the "140 patent"),
22 which is also entitled "Enhancer for Eukaryotic Expression Systems."¹ The patents-in-suit relate to
23 using certain DNA sequences known as enhancers that were identified in human cytomegalovirus
24

25 _____
26 ¹ Defendants' expert Dr. Levine explains the distinction between prokaryotic and eukaryotic
27 organisms as follows: "Generally, prokaryotic organisms are simpler than eukaryotic organisms.
28 Bacteria such as *E. coli* are examples of prokaryotic organisms. Eukaryotic organisms range from fairly
simple – yeast, for example – to very complex, such as humans. Typically, the DNA of an organism
is organized into one or more chromosomes. Prokaryotes typically have a single chromosome, while
eukaryotes typically have multiple chromosomes. A distinguishing feature of eukaryotic organisms is
that they have a discrete nucleus containing their chromosomes." Levine Decl. ¶ 13.

1 (“HCMV”). Sanofi alleges that Biogen and Genentech have infringed the ‘522 and ‘140 patents by
2 using the patented enhancers in the manufacture and sale of two pharmaceuticals, Rituxan® and
3 Avastin®.

4 Deoxyribonucleic acid (DNA) contains the genetic code for all living organisms. To turn this
5 code into proteins that can actually be used by a given organism, the completion of a multi-step process
6 is required. Within an individual cell, the DNA is first “transcribed” into ribonucleic acid (RNA).
7 Transcription is performed by a molecule called RNA Polymerase, which “reads” the DNA and helps
8 to produce a complementary RNA strand. Once the complementary RNA strand has been produced,
9 it is “translated” by cellular structures called ribosomes. Ribosomes decode the RNA into amino acids,
10 which are the building blocks of proteins.

11 An enhancer is a segment of DNA that, along with associated proteins, can serve to increase the
12 transcription of RNA from DNA. Enhancers are thought to act in concert with RNA Polymerase and
13 other molecules called transcription factors to promote transcription. Some of the strongest known
14 enhancers have been derived from viruses, which attack other organisms by taking over the cellular
15 machinery and using it to produce proteins that the virus needs in order to reproduce. Although
16 enhancers are often found immediately upstream² of the affected gene, they can also be effective despite
17 being located thousands of base-pairs³ away. Developments in biotechnology in the last thirty years
18 have led to the use of enhancers in the production of pharmaceutical products. If an enhancer can be
19 artificially introduced into a cell that produces a drug, that cell will be able to produce the drug at a
20 much higher rate than would normally be possible. The level of efficiency created by genetic enhancers
21 is, in part, what makes large scale pharmaceutical production possible.

22 Sanofi’s predecessor, Behringwerke AG, filed the original U.S. application for the ‘522 and ‘140
23

24 ² The terms “upstream” and “downstream” are a means of describing directionality on a strand
25 of DNA. When looking at a diagram of a DNA sequence, “upstream” is equivalent to the “5' direction”
or “left,” and “downstream” is equivalent to the “3' direction” or “right.”

26 ³ The term “base-pair” is a reference to the structure of DNA. DNA is a double-stranded
27 molecule; the two strands come together through the binding of two complementary base pairs. A DNA
28 molecule may consist of thousands of base-pairs, connected into a long strand. Base-pairs are the
default measure of distance on a DNA strand, which scientists can use to specify the location of a
genetic element.

1 patents on August 23, 1985.⁴ The two patents share the same six inventors and the same single-page
 2 specification. The patents were prosecuted for more than a decade, with the '522 patent issuing in 1998
 3 and the '140 patent issuing in 2001.

4 On August 6, 1992, Sanofi and Genentech entered into a license agreement which gave
 5 Genentech a nonexclusive license to a patent portfolio including the '522 and '140 patents.⁵ In
 6 exchange for the license, Genentech was obligated to pay an annual fee to use the patents for research
 7 purposes, as well as royalties on all commercial products that utilized the patents. Genentech made the
 8 annual payments until 2008, but never paid Sanofi royalties. On June 30, 2008, Sanofi sent Genentech
 9 a request for information about whether any of Genentech's commercial products utilized the patents,
 10 and also to request that Genentech pay royalties due for such products. Genentech provided notice to
 11 Sanofi that the License Agreement was terminated, effective on October 27, 2008.

12 On October 27, 2008, Sanofi filed a complaint in the U.S. District Court for the Eastern District
 13 of Texas against defendants Biogen and Genentech alleging infringement of the HCMV enhancer
 14 patents. The same day, Genentech and Biogen filed a complaint in the Northern District of California
 15 requesting declaratory judgment of invalidity and non-infringement of the HCMV enhancer patents.
 16 Those two actions have been consolidated and are now before this Court.

18 LEGAL STANDARD

19 Claim construction is a matter of law. *Markman v. Westview Instr., Inc.*, 517 U.S. 370, 372
 20 (1996). Terms contained in claims are "generally given their ordinary and customary meaning."
 21 *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). "[T]he ordinary and customary meaning
 22 of a claim term is the meaning that the term would have to a person of ordinary skill in the art in
 23 question at the time of the invention." *Id.* at 1312. In determining the proper construction of a claim,
 24 a court begins with the intrinsic evidence of record, consisting of the claim language, the patent

26 ⁴ The patents originated from a German Patent Application No. DE 34 31 140.8, which was filed
 27 with the German Patent Office on August 24, 1984.

28 ⁵ At the hearing, counsel stated that it was their understanding that the license agreement was
 for the prospective use of the patents when the patents issued.

1 specification, and, if in evidence, the prosecution history. *Id.* at 1313; *see also Vitronics Corp. v.*
2 *Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). “The appropriate starting point . . . is always
3 with the language of the asserted claim itself.” *Comark Communications, Inc. v. Harris Corp.*, 156 F.3d
4 1182, 1186 (Fed. Cir. 1998); *see also Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1023 (Fed. Cir.
5 1997).

6 Accordingly, although claims speak to those skilled in the art, in construing a claim, claim terms
7 are given their ordinary and accustomed meaning unless examination of the specification, prosecution
8 history, and other claims indicates that the inventor intended otherwise. *See Electro Medical Systems,*
9 *S.A. v. Cooper Life Sciences, Inc.*, 34 F.3d 1048, 1053 (Fed. Cir. 1994). The written description can
10 provide guidance as to the meaning of the claims, thereby dictating the manner in which the claims are
11 to be construed, even if the guidance is not provided in explicit definitional format. *SciMed Life*
12 *Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, 242 F.3d 1337, 1344 (Fed. Cir. 2001). In other
13 words, the specification may define claim terms “by implication” such that the meaning may be “found
14 in or ascertained by a reading of the patent documents.” *Vitronics*, 90 F.3d at 1584 n.6.

15 The claims must be read in view of the specification. *Markman*, 52 F.3d at 978. Although
16 claims are interpreted in light of the specification, this “does not mean that everything expressed in the
17 specification must be read into all the claims.” *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 957 (Fed.
18 Cir. 1983). For instance, limitations from a preferred embodiment described in the specification
19 generally should not be read into the claim language. *See Comark*, 156 F.3d at 1187. However, it is
20 a fundamental rule that “claims must be construed so as to be consistent with the specification.”
21 *Phillips*, 415 F.3d at 1316. Therefore, if the specification reveals an intentional disclaimer or disavowal
22 of claim scope, the claims must be read consistent with that limitation. *Id.*

23 Finally, the Court may consider the prosecution history of the patent, if in evidence. The
24 prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was
25 disclaimed during prosecution. *See Southwall Technologies, Inc. v. Cardinal IG Co.*, 54 F.3d 1570,
26 1576 (Fed. Cir. 1995). In most situations, analysis of this intrinsic evidence alone will resolve claim
27 construction disputes. *See Vitronics*, 90 F.3d at 1583. Courts should not rely on extrinsic evidence in
28 claim construction to contradict the meaning of claims discernable from examination of the claims, the

written description, and the prosecution history. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1308 (Fed. Cir. 1999) (citing *Vitronics*, 90 F.3d at 1583). However, it is entirely appropriate “for a court to consult trustworthy extrinsic evidence to ensure that the claim construction it is tending to from the patent file is not inconsistent with clearly expressed, plainly apposite, and widely held understandings in the pertinent technical field.” *Id.* Extrinsic evidence “consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises.” *Phillips*, 415 F.3d at 1317. All extrinsic evidence should be evaluated in light of the intrinsic evidence. *Id.* at 1319.

DISCUSSION

The parties dispute terms contained within claim 1 of the ‘522 patent, and claims 42, 43 and 45 of the ‘140 patent. In order to construe the disputed terms, the Court must define a person of ordinary skill in the art around the time of the invention, which is the early to mid-1980s. The parties agree that a person of ordinary skill in the art during this time frame is a doctoral graduate student or post-doctoral fellow in molecular biology, molecular genetics or a similar field. Levine Decl. ¶ 34; Sanofi’s Response to Interrogatory No. 6 (Kokjohn Decl. Ex. 16). Such a person would be conversant with the techniques of recombinant DNA technology, including the use of restriction enzymes to fragment and isolate pieces of DNA, ligation (linking together two or more pieces of DNA), DNA sequence analysis, gene expression systems, and transfection (introducing DNA into cells). *Id.*

I. ‘522 Patent, Claim 1

Claim 1 of the ‘522 patent reads as follows, with the disputed claim terms in bold:

1. A method to increase expression of a gene in a mammalian cell comprising inserting into a mammalian cell an isolated DNA enhancer consisting of DNA from the upstream region of the major immediate early (IE) gene of the human cytomegalovirus (HCMV) and a heterologous gene that is to be expressed, wherein the DNA from the upstream region of the IE gene of HCMV is the only HCMV material to which the mammalian cell is exposed.

A. “isolated DNA enhancer”

Sanofi argues that “isolated DNA enhancer” means “a DNA sequence, separated from its

1 original source by human intervention, capable of: (1) strongly activating transcription of a linked gene,
2 (2) functioning independent of orientation and (3) functioning even if located long distances upstream
3 or downstream relative to the initiation site of the linked gene.” In support of its construction, Sanofi
4 relies on language in the specification stating “A process for improvement of eukaryotic expression
5 systems by incorporating the enhancer upstream or downstream of the structural gene or of the
6 regulation region is also provided.” ‘522 patent, col. 1, lines 24-27; that the enhancer of the invention
7 “enhances the expression of rabbit betaglobin . . . by at least two orders of magnitude, irrespective of
8 the orientation,” *id.* at lines 57-60; and that “the enhancer is superior to that of SV40 by the factor 3 to
9 5, dependent on the host system,” *id.* at 60-62.

10 Sanofi also relies on the prior art cited in the ‘522 patent, which set forth the criteria of enhancers
11 as including the ability to increase transcriptional efficiency in a manner relatively independent of
12 position and orientation with respect to a nearby gene. *See, e.g.*, Wall Decl. ¶ 38; Kokjohn Ex. 6 (Julian
13 Banerji *et al.*, *Expression of a β -Globin Gene Is Enhanced by Remote SV40 DNA Sequences*, 27 Cell
14 299, 299 (Dec. 1981) (noting a “200-fold increase in the level of correctly initiated transcripts from a
15 rabbit β -globin gene” when the gene is linked to the enhancer DNA and noting that “the viral ‘enhancer’
16 can act over very long distances, and independent of its orientation”); Kokjohn Ex. 8 (Frank Weber *et al.*,
17 *An SV40 “Enhancer Trap” Incorporates Exogenous Enhancers or Generates Enhancers from Its*
18 *Own Sequences*, 36 Cell 983, 983 (Apr. 1984) (“Transcriptional enhancers are short DNA segments that
19 activate the transcription of linked genes, in either orientation and over distances of many kilobase pairs
20 (kb)”). The Court finds that the intrinsic evidence supports a construction that includes the three
21 functional criteria identified by Sanofi.

22 Defendants initially proposed “a regulatory DNA fragment, distinct from promoter DNA, that
23 causes more production of RNA from DNA.” In response to questioning from the Court at the claim
24 construction hearing, defendants proposed the following compromise construction that combined
25 elements of both parties’ constructions: “a DNA sequence, separated by human intervention from the
26 promoter DNA in its original source, that (1) strongly stimulates transcription of a linked gene, (2)
27 functions independent of orientation, and (3) functions even if located long distances upstream or
28 downstream relative to the initiation site of the linked gene.”

Although defendants' proposed compromise construction incorporates the three functional criteria that Sanofi asserts are critical to defining an "enhancer," Sanofi would not agree to the proposed construction because Sanofi contends that the "isolated DNA enhancer" sequence could, but need not, also include the promoter. Sanofi did not offer any argument in support of this contention, and the Court concludes that the intrinsic evidence does not support a construction of "isolated DNA enhancer" that includes the promoter. The only enhancers described in the specification, "C2" and "C4," do not include the promoter. The specification states,

Two recombinants were isolated by sonication of the DNA from the IE region of HCMV with the formation of about 300 bp fragments, co-transfection of CV1 monkey cells and enhancerless SV40 genome, isolation of the recombinants which show lytic growth, and isolation of the inserted HCMV DNA, and enhancer-active mutants of this DNA. Those recombinants contained 341 and 262 bp of HCMV DNA, located at positions -118 to -458 and -263 to -524 respectively on the published DNA sequence (Greenaway et al., loc. cit.).

'522 patent, col. 1, lines 40-49 (italics added). The "recombinants" that were isolated are the two enhancers, "C2" and "C4." Figure 1a shows the location of the two enhancers, "C2" and "C4," which are both upstream of the native HCMV promoters, denoted by "C" and "T." Similarly, Figure 1b, which provides DNA sequence information, shows that the "C2" and "C4" enhancers are upstream from, and do not include, the promoters. Moreover, during the patent prosecution, the applicants relied on the distinction between a promoter and an enhancer to overcome an obviousness rejection.

. . . the enhancer activity of the claimed DNA is an "essential element" which is not disclosed in Thomsen or Jahn. Thus, the rejection regarding these two references is in error.

Applicants also note that both Jahn and Thomsen relate to the possible existence of a promoter element in the immediate early region of HCMV, but a promoter is not an enhancer. This fact is apparent from the Thomsen article in which the authors focused their attention on the possible "cruciform" structure The cruciform structure is not the enhancer. . . .

Gross Decl. Ex. 24 at 9.

Accordingly, the Court defines "isolated DNA enhancer" as "a DNA sequence, separated by human intervention from the promoter DNA in its original source, that (1) strongly stimulates transcription of a linked gene, (2) functions independent of orientation, and (3) functions even if located long distances upstream or downstream relative to the initiation site of the linked gene."

B. “DNA from the upstream region of the major immediate early (IE) gene of human cytomegalovirus (HCMV)”

Sanofi contends that this term means “DNA from a portion of the major immediate early (IE) gene of human cytomegalovirus (HCMV) that is located upstream of the coding region of that gene.” Genentech and Biogen assert that the proper construction is “DNA from the region that is upstream of the transcription start site of the major IE gene of HCMV.”

The parties’ dispute centers on where to set the downstream boundary of the “upstream region.” Sanofi believes that the downstream boundary should be the beginning of the coding region of the gene, known as the translation start site, whereas Genentech and Biogen argue that the downstream boundary should be the transcription start site. The difference between the two boundaries is an approximately 950 base-pair segment of HCMV DNA called the “non-coding transcribed region.” *See Levine Decl.* ¶ 30.

The parties agree that “DNA from the upstream region of the major immediate early (IE) gene of human cytomegalovirus (HCMV)” defines where a person of ordinary skill in the art will find the DNA enhancer of the invention. Sanofi relies on the statement in the specification that the “enhancer is located in the HindIII E fragment, which includes the PstI m fragment (about 2.1 kb).” ‘522 patent, col. 1, lines 36-39 (internal citation omitted). Sanofi argues that because one end of the PstI m fragment is located immediately upstream of the translation start site, the downstream boundary of the “upstream region of the major immediate early IE gene” should be located at the downstream terminus of the PstI m fragment.

Sanofi’s proposed construction is not persuasive for a number of reasons. As an initial matter, claim 1 does not mention the PstI m fragment. Although the specification states that the enhancer is located in the PstI m fragment, the specification does not associate the “upstream region” with either end of the PstI m fragment. Moreover, it is undisputed that the two enhancers, “C2” and “C4,” are located in the portion of the PstI m fragment upstream from the transcription start site.⁶ It is also

⁶ The parties agree that the “PstI m fragment of the immediate early (IE) region of human cytomegalovirus (HCMV)” means “the DNA fragment bounded at one end by the first PstI restriction enzyme upstream of the transcription start site of the major immediate early gene, and at the other end by the first PstI restriction enzyme site downstream of the transcription start site of the major immediate

undisputed that there are no enhancers located in the 950 base-pair segment between the transcription start site and the translation start site. Simply because the PstI m fragment includes this 950 base-pair segment does not mean that “DNA from the upstream region of the major immediate early (IE) gene of human cytomegalovirus (HCMV)”– which defines where the DNA enhancer is found – should be defined to include a segment that indisputably does not contain the C2 and C4 enhancers. Notably, Sanofi does not provide any expert testimony in support of its construction.

Sanofi also argues that its construction is correct because while claim 1 uses the language “DNA from the upstream region of the IE gene” of HCMV, claim 2 uses the phrase “DNA from the PstI restriction enzyme site upstream of the transcription start site.” Sanofi argues that if the applicants had intended the language in claim 1 to mean the region upstream of the transcription start site, the applicants would have used the term “transcription start site,” as they did in claim 2. While at first blush this argument has some force, the use of “transcription start site” in claim 2 must be read in the context of the entirety of claim 2. Claim 2 reads,

The method as claimed in claim 1, wherein the DNA enhancer consists of the DNA from the PstI restriction enzyme site upstream of the transcription start site to position -118 of the PstI-m fragment, or an enhancer-active part thereof.

‘522 patent, col. 3, lines 4-8. In claim 2, “transcription start site” is used to denote one of the two ends of the PstI m fragment. Claim 2 specifies an upstream boundary (“the PstI restriction enzyme site upstream of the transcription start site) and a downstream boundary (“position -118 of the PstI-m fragment”), and specifies that the DNA enhancer consists of the DNA from that segment. In contrast, claim 1 does not specify an upstream boundary, and thus the absence of “transcription start site” in claim 1 is not meaningful in the way Sanofi suggests.

Defendants contend that the specification and file history of the ‘522 patent demonstrate that “upstream region” refers to the region upstream of the transcription start site. The Court agrees. There is no dispute that those skilled in the art understood that base pairs in DNA are numbered with negative numbers upstream of +1, and positive numbers downstream of +1, and that +1 is the transcription start site. *See* Levine Decl. ¶ 31; *see also* Wall Decl. ¶ 21. The Court finds it significant that Figure 1a

early gene.”

demarcates the beginning of the transcription start site (labeled “CAP”), but does not identify the translation start site. The two identified enhancers, “C2” and “C4,” are both located well upstream of the transcription start site. Importantly, Figures 1a and 1b only show a small portion of the non-coding transcribed region that Sanofi contends should be included in the “upstream region”; the inventors never sequenced most of the DNA in the 950 base-pair segment of the non-coding transcribed region that Sanofi contends should be included in the “upstream region.”

Defendants’ construction also finds support in statements made by the inventors during depositions. In a deposition, inventor Michael Boshart was asked if, at the time the research behind the patent was being conducted, he would have expected to find any enhancer activity downstream of the C2 fragment. Gross Decl., Ex. 10 at 119:15. He responded that “[t]here was no enhancer activity downstream . . . because there you reach already the basic promoter elements, and enhancers have been defined as promoter upstream regulatory elements.” *Id.* at 119:25-120:4. Similarly, inventor Gerhard Jahn testified that the “upstream region” was located upstream of the promoter’s “TATAA” box (in Figure 1a), which is located immediately upstream of the transcription start site. *Id.* Ex. 9 at 112:11-113:6.

Accordingly, the Court construes “DNA from the upstream region of the major immediate early (IE) gene of human cytomegalovirus (HCMV)” as “DNA from the region that is upstream of the transcription start site of the major IE gene of HCMV.”

C. “wherein the DNA from the upstream region of the IE gene of HCMV is the only HCMV material to which the mammalian cell is exposed.”

Sanofi argues that the above term should be interpreted to mean “the mammalian cell is not exposed to material from HCMV (such as virions and/or dense bodies) other than HCMV DNA.” The main source of support offered by Sanofi for this interpretation is the patent prosecution history. Following the rejection of the ‘658 patent application (a predecessor to the ‘522 patent), the applicants conducted a phone interview with the applicants in during which they decided to “claim a method that would exclude exposing the mammalian host cell to HCMV virions or particles as taught by Stinski.” Kokjohn Ex. 11 at 2-3. The language used in the proposed amendment to the ‘658 patent, made shortly

1 after this conversation, was identical to the language at issue here.

2 Defendants contend that no construction is necessary. Defendants assert that because the Court
3 is separately construing the phrase “DNA from the upstream region of the IE gene,” the dispute on this
4 term is limited to the meaning of “the only HCMV material.” Defendants argue that “the only HCMV
5 material” has no specialized meaning in the art, and thus the phrase “the only HCMV material” should
6 be presumed to carry its ordinary and accustomed meaning. Defendants argue that the term requires that
7 the separately construed “DNA from the upstream region of the IE gene” is “the only HCMV material”
8 to which the mammalian cell is exposed. Defendants argue that Sanofi’s proposed construction – that
9 the cell is “not exposed to material from HCMV . . . other than HCMV DNA” – improperly reads the
10 “from the upstream region of the IE gene” limitation out of the claim.

11 The Court agrees with defendants that no construction of this term is necessary. The Court has
12 already defined the term “DNA from the upstream region of the IE gene of HCMV,” to which “the only
13 HCMV material” refers. “The only HCMV material” does not have any specialized scientific meaning.
14 Sanofi’s proposed construction is not based on the claim language or the specification. While Sanofi’s
15 construction finds some support in the patent prosecution, Sanofi’s construction eliminates the claim’s
16 requirement of an enhancer “consisting of” DNA from the specific upstream region of the IE gene by
17 permitting using any HCMV DNA from any region. *See Vehicular Techs. Corp. v. Titan Wheel Int’l,*
18 *Inc.*, 212 F.3d 1377, 1382-83 (Fed. Cir. 2000) (“The phrase “consisting of” is a term of art in patent law
19 signifying restriction and exclusion, while, in contrast, the term “comprising” indicates an open-ended
20 construction. . . . In simple terms, a drafter uses the phrase “consisting of” to mean “I claim what follows
21 and nothing else.”) (internal citations omitted). Sanofi’s construction also does not make scientific
22 sense because, as Sanofi acknowledged at the hearing, virions in fact contain HCMV DNA. *See also*
23 *Levine Decl.* ¶ 53 (“[I]t was well established in the relevant time frame that HCMV ‘virions’ include
24 HCMV DNA.”).

25 26 **II. ‘140 Patent, Claims 42, 43 and 45**

27 Claims 42, 43 and 45 of the ‘140 patent read as follows, with the disputed terms in bold:

28 **42. A recombinant DNA plasmid** comprising a DNA molecule isolated from the

immediate early (IE) promoter/regulatory region of human cytomegalovirus (HCMV) and a heterologous gene positioned downstream and operatively linked to said molecule, wherein the DNA molecule enhances the transcription of DNA in an animal or mammalian host cell expression system.

43. A eukaryotic host cell transformed with a **recombinant DNA plasmid** comprising a DNA molecule isolated from the **immediate early (IE) promoter/regulatory region** of human cytomegalovirus (HCMV) and a heterologous gene positioned downstream and operatively linked to said DNA molecule, **wherein the DNA molecule enhances the transcription of DNA** in an animal or mammalian host cell expression system.

45. A **recombinant DNA plasmid** comprising a DNA molecule isolated from the PstI m fragment of the immediate early (IE) region of human cytomegalovirus (HCMV) and a heterologous gene positioned downstream and operatively linked to said DNA molecule, **wherein said DNA molecule enhances expression of said heterologous gene.**

A. “recombinant DNA plasmid” (claims 42, 43 and 45)

All parties agree that “recombinant DNA” means “DNA from two or more sources.” Therefore, the only portion of the term in dispute is “plasmid.” Sanofi contends that “plasmid” means “an autonomous DNA molecule.”⁷ Genentech does not believe that the term requires construction, while Biogen contends that the proper definition of “plasmid” is a “circular, extrachromosomal molecule.”

The term “recombinant DNA plasmid” does not appear anywhere in the specification. However, in the sole example set forth in the specification, the inventors refer to two plasmids by name (“pUC 8” and “pβx14”) rather than by the term “plasmid.” ‘140 patent, col. 2, lines 41-54. The parties agree that these two plasmids fit Biogen’s definition of “circular, extrachromosomal molecule,” although Sanofi asserts that these examples cannot be read as a limitation of the claims.

It is undisputed that the term “recombinant DNA plasmid” was copied from U.S. Patent No. 5,168,062, issued on December 1, 1992 to Dr. Stinski (the “Stinski Patent”).⁸ Biogen argues that

⁷ As discussed *infra*, Sanofi acknowledges that its expert, Dr. Wall, does not believe that Sanofi’s proposed definition accurately reflects the use of the term plasmid as that term is used by those of ordinary skill in the art. See Wall Decl. ¶ 44. (Dr. Wall also criticizes Biogen’s proposed construction.) Sanofi’s opening claim construction brief also states that “it is willing to modify the proposed language used to define the term ‘plasmid’ to more accurately reflect the ordinary meaning and common usage of the term by those of skill in the art in the mid 1980s,” but Sanofi did not propose an alternate construction. Sanofi’s Opening Claim Construction Brief at 19:8-11.

⁸ During the prosecution of U.S. Application 07/285,330, the Patent Office rejected the claims as anticipated and made obvious by the Stinski Patent. Gross Decl. Ex. 20. On November 30, 1993, the applicants copied claims from the Stinski Patent into their application in an attempt to provoke an

1 because the ‘140 specification does not define “plasmid,” the Court should be guided by the Stinski
2 Patent in defining this term. The Stinski Patent defines a “plasmid” as the following:

3 Plasmid is the term applied to any autonomously replicating DNA unit which might be
4 found in a microbial cell, other than the genome of the host cell itself. A plasmid is not
5 genetically linked to the chromosome of the host cell. Plasmid DNA’s exist as double
6 stranded ring structures

7

8 Plasmid DNA exists as a closed ring.

9 Younkin Decl. Ex. A (Stinski Patent) at col. 3, lines 1-19. Biogen notes that during the prosecution of
10 the ‘140 patent, the Patent Office and the applicants treated Stinski’s “recombinant DNA plasmid” and
11 the applicants’ “recombinant DNA plasmid” as the same thing. *See* Younkin Decl. Ex. C at 2.

12 Biogen also contends that its construction is supported by extrinsic evidence. Biogen’s expert
13 Dr. Hauschka states that plasmids were originally discovered in bacteria, as circular pieces of DNA that
14 were separate from the cell’s own chromosome. Hauschka Decl. ¶ 7. Dr. Hauschka states that “in the
15 1980s, and also today, if a molecular biologist were asked to visualize a ‘recombinant DNA plasmid,’
16 the molecular biologist would envision a circular, extra-chromosomal DNA molecule including DNA
17 from two or more sources.” *Id.* ¶ 14. Dr. Hauschka provides a detailed explanation for this opinion.
18 *Id.* ¶¶ 7-13. Biogen also cites a number of contemporaneous sources in support of its construction. *See,*
19 *e.g.,* T. Maniatis *et al.*, *Molecular Cloning: A Laboratory Manual*, 3 (1982) (“Plasmids are
20 extrachromosomal genetic elements found in a variety of bacterial species. They are double-stranded,
21 closed circular DNA molecules that range in size from 1 kb to greater than 200 kb.”) (Younkin Decl.
22 Ex. D); Bruce Alberts *et al.*, *Molecular Biology of the Cell*, 187 (1983) (“Plasmids are small circular
23 molecules of double-stranded DNA that occur naturally in both bacteria and yeast, where they replicate
24 as independent units as the host cell proliferates.”) (Younkin Decl. Ex. E); Harvey Lodish *et al.*,
25 *Molecular Cell Biology*, 248-49 (1986) (stating a plasmid is a “small circular DNA molecule capable
26 of reproducing independently within a bacterial host”) (Younkin Decl. Ex. G); Benjamin Lewin, *Genes*,
27 679 (1983) (defining plasmid as “an autonomous self-replicating extrachromosomal circular DNA”)

28 interference. *Id.* Ex. 23 at 1-2. The interference was never provoked. However, the language copied
from Stinski Patent remains in the language of claims 42, 43 and 45 of the ‘140 patent.

(Younkin Decl. Ex. H).

The Court agrees with Biogen’s construction and finds that it is supported by the intrinsic and extrinsic evidence. In the absence of any explicit guidance in the ‘140 patent regarding the term “plasmid,” the Stinski patent is important intrinsic evidence for this term. *See Kumar v. Ovonic Battery Co.*, 351 F.3d 1364, 1368 (Fed. Cir. 2003). The two plasmid examples contained in the specification are circular, extrachromosomal molecules, and thus there is nothing inconsistent about using the Stinski definition of plasmid to define “plasmid” in the ‘140 patent. Sanofi argues that Biogen’s definition is impermissibly limiting, yet Sanofi has not identified any intrinsic evidence or contemporaneous sources supporting a different construction, nor has Sanofi identified any inconsistency between the intrinsic evidence and Biogen’s construction.

Sanofi contends that Biogen’s construction is too narrow because it does not address the situation in which a plasmid is inserted into a eukaryotic cell. However, the Stinski Patent claims transforming a eukaryotic cell with a plasmid, and defines “plasmid” as a circular, extrachromosomal molecule. Moreover, as Dr. Hauschka explains, “[d]efining a ‘recombinant DNA plasmid’ as a ‘circular, extra-chromosomal molecule comprising DNA from two or more sources’ does not exclude the use of a recombinant DNA vector for the stable transformation of cell lines so that the DNA originating from the plasmid integrates into the host cell line’s chromosomal DNA.” Hauschka Decl. ¶ 14.

Once the foreign DNA had been integrated into chromosomal DNA, however, it was no longer “a recombinant DNA plasmid.” One might use the term “plasmid DNA” to indicate that the DNA in question originated from a plasmid, but that term does not mean that the DNA, once incorporated, is still a plasmid. When incorporated into a eukaryotic chromosome, the plasmid DNA would lose essential characteristics of a plasmid, including its extra-chromosomal existence and ability to replicate extra-chromosomally and independently of the cell life cycle.

Id. ¶ 12.

Sanofi also argues that Biogen’s construction contradicts its proposed construction of a different term – “a plasmid vector” – in a different patent. The Court finds this argument unpersuasive for several reasons. First, the probative value of Biogen’s proposed construction of a different term in a different patent with a different file history is minimal at best. Second, as Biogen notes, the patent at issue in *Biogen, Inc. v. Amchem Inc.*, 18 F. Supp. 2d 105 (D. Mass 1998), contained a definition of the term

1 “plasmid” that included the adjective “nonchromosomal.” Younkin Decl. Ex. 1 (U.S. Patent No.
2 4,874,702, col. 5, lines 60-62). In addition, every plasmid in the specification of that patent is circular.
3 *Id.*

4 Finally, Sanofi contends that Biogen’s construction is somehow inconsistent with Biogen’s 1997
5 FDA filing concerning Rituxan®. Sanofi argues that in its submissions to the FDA for Rituxan®,
6 Biogen provided data to the FDA regarding the numbers of copies of “Plasmid” containing the HCMV
7 enhancer and the heterologous genes for the Rituxan® protein that were integrated into the DNA of the
8 host cell expression system used to produce Rituxan®. Biogen responds that the term “plasmid copy
9 number” in the FDA filing refers to the number of copies of the DNA originating from the plasmid that
10 have integrated into the cell, and that “plasmid copy number” is not equivalent to “recombinant DNA
11 plasmid.” The Court finds nothing obviously inconsistent between the fact of Biogen’s 1997 FDA filing
12 and the proposed construction.

13 Accordingly, the Court construes “recombinant DNA plasmid” as “circular, extrachromosomal
14 molecule comprising DNA from two or more sources.”

15
16 **B. “immediate early (IE) promoter/regulatory region of human cytomegalovirus**
17 **(HCMV)” (claims 42 and 43)**

18 Sanofi’s preferred construction of this term is “the region upstream of the coding region of the
19 major immediately early (IE) gene of human cytomegalovirus (HCMV) that regulates the transcription
20 of that gene.” Sanofi’s definition would encompass DNA starting at the translation start point and
21 extending upstream without any upstream boundary. Defendants advocate for a significantly narrower
22 construction: “the approximately 490-base-pair region of DNA that is immediately upstream of the
23 transcription start site of the major immediate early gene of HCMV.” Defendant’s definition would
24 encompass the region of DNA starting at the transcription start site and extending 490 base-pairs
25 upstream. Thus, the parties disagree both about the downstream boundary of the “IE
26 promoter/regulatory region” of HCMV – the transcription start site (defendants) vs. the translation start
27 site (Sanofi) – as well as the upstream boundary of the promoter/regulatory region – 490 base-pairs
28 upstream of the transcription start site (defendants) vs. no upstream boundary (Sanofi).

1 The parties agree that the phrase at issue was only added to the patent to preserve the applicants’
2 right to provoke an interference against the Stinski patent. To provoke an interference, the proposed
3 patent needed to have claims that were identical to the Stinski patent. Defendants argue that since the
4 phrase was intentionally copied from the Stinski patent, the same definition of “immediate early (IE)
5 promoter/regulatory region” that was used in the Stinski patent should be used here. The Stinski patent
6 contains a figure with a map of the promoter/regulatory region of the IE gene, which indicates that the
7 promoter/regulatory region is approximately 490 base-pairs long. Levine Decl., Ex. 3 at 4.

8 The Court finds that neither of the definitions proposed by the parties is correct. Claim 1 of the
9 ‘140 patent refers to an isolated DNA enhancer, which runs from either position -458 to -118 or position
10 -524 to -263 of the upstream region of the IE gene. ‘140 patent, Figs. 1a & 1b. Claims 42, 43 and 45
11 refer to this same enhancer, but in these claims the enhancer, along with a target gene, is part of a
12 plasmid. Since an enhancer is by definition part of the regulatory region of a gene, and the patented
13 enhancer extends to position -524, the Court finds that the upstream boundary of the “immediate early
14 (IE) promoter/regulatory region of human cytomegalovirus (HCMV)” extends to approximately position
15 -524 as well. The Court does not adopt the Stinski patent’s definition of “promoter/regulatory region”
16 because under that definition, the upstream boundary is located in the middle of the identified C4
17 enhancer, and thus would not include one of the two enhancers that are the subject of the invention.

18 The conflict between the parties regarding the downstream boundary of the promoter/regulatory
19 region echoes the dispute over the term “DNA from the upstream region of the major immediate early
20 (IE) gene of human cytomegalovirus (HCMV),” discussed *supra*. Sanofi argues that the downstream
21 boundary should be linked to the downstream terminus of the PstI m fragment, yet claims 42 and 43 do
22 not recite the PstI m fragment. In addition, the specification makes no mention of a coding region, the
23 applicants never sequenced the DNA that extends to the coding region, and the only two enhancer
24 fragments described in the specification, C2 and C4, are both entirely upstream of the transcription start
25 site. The Court finds that the location of the patented enhancer fragments, coupled with the
26 understanding of scientists skilled in the art at the time, indicates that the transcription start site is the
27 proper downstream boundary.

28 Accordingly, the Court construes “immediate early (IE) promoter/regulatory region of human

cytomegalovirus (HCMV)” as “the approximately 524-base-pair region of DNA that is immediately upstream of the transcription start site of the major immediate early gene of HCMV.”

C. “wherein the DNA molecule enhances the transcription of DNA” (claims 42 and 43)
“wherein said DNA molecule enhances expression of said heterologous gene.”
(claim 45)

Claims 42, 43 and 45 claim plasmids comprising a DNA molecule, “wherein the DNA molecule enhances the transcription of DNA” (claims 42 and 43) or “wherein said DNA molecule enhances expression” (Claim 45). Sanofi contends that the term in claims 42 and 43 means “the DNA molecule acts as an enhancer, capable of: (1) strongly activating transcription of a linked gene, (2) functioning independent of orientation, and (3) functioning even if located long distances upstream or downstream relative to the initiation site of the linked gene, to increase the rate of transcription of the heterologous gene above a basal level for that gene.” Sanofi’s proposed definition for term in claim 45 contains the same language, with the addition of the clause “which results in an increase in the amount of protein coded by that heterologous gene to be produced.” At the claim construction hearing, Sanofi clarified its position that the “DNA molecule” in this term should be construed to be an “enhancer.”

In contrast, defendants contend that “wherein the DNA molecule enhances the transcription of DNA” in claims 42 and 43 means “wherein the DNA molecule causes more production of RNA from DNA.” For claim 45, defendants propose the same language, with the addition of “and more production of protein, from the heterologous gene.”

The Court adopts defendants’ constructions. Defendants’ constructions define transcription and expression, and the parties are in basic agreement on how to define these processes. The Court agrees with defendants that there is no need to define “DNA molecule.” In the three claims, “the DNA molecule” (claims 42 and 43) and “said DNA molecule” (claim 45) refer back to antecedents in the claim. The antecedent in claims 42 and 43 is “a DNA molecule isolated from the immediately early (IE) promoter/regulatory region” of HCMV. ‘140 patent, col. 5, lines 1-3 and 9-11. In claim 45, the antecedent is “a DNA molecule isolated from the PstI m fragment of the immediate early (IE) region of human cytomegalovirus (HCMV).” *Id.*, col. 6, lines 5-7. There is nothing in the antecedent language

1 that limits the “DNA molecule” only to an “enhancer.” Instead, the “DNA molecule” in claims 42 and
 2 43 is isolated from the “promoter/regulatory region,” which could include all or part of the promoter.
 3 The “DNA molecule” in claim 45 is isolated from the “PstI m fragment,” which is approximately 2,000
 4 base-pairs and includes DNA sequences other than just an enhancer.

5 The prosecution history also does not support Sanofi’s construction of the “DNA molecule” as
 6 limited to an enhancer. The parties agree that the claims of the ‘140 patent were copied from the Stinski
 7 Patent. As discussed *supra*, the applicants distinguished claim 1 of the ‘522 patent, which uses the
 8 language “isolated DNA enhancer,” from the Stinski patent by arguing that their “enhancer” was
 9 different from the “promoter” portion of Stinski’s “promoter-regulatory region.” Gross Decl. Ex. 24
 10 at 9. In addition, during the prosecution of the ‘140 patent, the applicants told the Patent Office that the
 11 claimed “DNA molecule” was broader than just an enhancer. On May 10, 1999, the applicants filed an
 12 appeal brief after failing to overcome an anticipating prior art reference, the Stinski patent.

13 The fact that Stinski may have identified a sequence that includes the enhancer
 14 does not establish that Stinski explicitly or necessarily disclosed each and every element
 15 of claim 56 [claim 42 in the ‘140 patent]. Claim 56 requires more elements than the
 DNA molecule isolated from the IE promoter/regulatory region of HCMV and is not
 even limited to such a molecule that is an enhancer.

16 Supp. Gross Decl. Ex. A at 12. Sanofi’s proposed construction of “DNA molecule” as consisting solely
 17 of the enhancer is inconsistent with these statements in the prosecution history, and thus cannot be
 18 adopted. *See Chimie v. PPG Industries, Inc.*, 402 F.3d 1371, 1384 (Fed. Cir. 2005).

19 There are several other problems with Sanofi’s proposed constructions. Sanofi is attempting to
 20 incorporate its construction of the noun phrase “isolated DNA *enhancer*” from the ‘522 patent into the
 21 verb phrase “wherein the DNA molecule *enhances*” Sanofi’s construction “is at war with its
 22 grammar and syntax and thus would force an unreasonable interpretation.” *Credle v. Bond*, 25 F.3d
 23 1566, 1571-72 (Fed. Cir. 1994). In addition, Sanofi’s construction includes the phrase “increases the
 24 rate of transcription.” However, neither the claims nor the specification mentions the “rate” of
 25 transcription. The specification refers only to increases in the amount of RNA and protein made by a
 26 cell.

27 Accordingly, in claim 43, the Court construes the term “wherein the DNA molecule enhances
 28 the transcription of DNA” as “wherein the DNA molecule causes more production of RNA from DNA.”

In claim 45, the term “wherein the DNA molecule enhances expression of said heterologous gene” means “wherein the DNA molecule causes more production of RNA from DNA, and more production of protein, from the heterologous gene.”

CONCLUSION

For the reasons stated above, the Court hereby adopts the following constructions:

‘522 patent, claim 1

- “isolated DNA enhancer” means “a DNA sequence, separated by human intervention from the promoter DNA in its original source, that (1) strongly stimulates transcription of a linked gene, (2) functions independent of orientation, and (3) functions even if located long distances upstream or downstream relative to the initiation site of the linked gene”
- “DNA from the upstream region of the major immediate early (IE) gene of human cytomegalovirus (HCMV)” means “DNA from the region that is upstream of the transcription start site of the major IE gene of HCMV”
- “wherein the DNA from the upstream region of the IE gene of HCMV is the only HCMV material to which the mammalian cell is exposed”: no construction is necessary

‘140 patent, claims 42, 43 and 45

- “recombinant DNA plasmid” means “circular, extrachromosomal molecule comprising DNA from two or more sources”
- “immediate early (IE) promoter/regulatory region of human cytomegalovirus (HCMV)” means “the approximately 524-base-pair region of DNA that is immediately upstream of the transcription start site of the major immediate early gene of HCMV”
- “wherein the DNA molecule enhances the transcription of DNA” means “wherein the DNA molecule causes more production of RNA from DNA”
- “wherein said DNA molecule enhances expression of said heterologous gene” means “wherein the DNA molecule causes more production of RNA from DNA, and more production of protein, from the heterologous gene”

IT IS SO ORDERED.

Dated: June 23, 2010



SUSAN ILLSTON
United States District Judge